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EXAMINER	
NEGIN, RUSSELL SCOTT	
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1631	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/087,441	PALSSON ET AL.	
	Examiner	Art Unit	
	Russell S. Negin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16 and 18-74* is/are pending in the application.

4a) Of the above claim(s) *66-69* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16,18-65 and 70-74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Comments

It is acknowledged that claim 17 is cancelled. Claims 1-16, 18-65, and 70-74 are examined in this Office action.

Priority

The arguments of the applicant concerning priority on page 14 of the Remarks of 8 November 2006 have been fully considered. They are found to be persuasive.

Accordingly, claims 1-74 are awarded the benefit date of 1 March 2001.

Specification

The objection to the specification as failing to provide proper antecedent basis for the claimed subject matter is withdrawn due to arguments made by applicant on pages 13 and 23-25 of the Remarks of 8 November 2006. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o).

Claim Rejections - 35 USC § 112

The rejection of claims 12-13, 30, 35-38, and 46-47 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn due to arguments made by applicant in pages 21-26 of the Remarks of 8 November 2006.

The rejection of claims 2-7, 9-16, 26-30, 32-33, 35-39, 48-50, 52, 55, 64-66, and 73 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention (i.e. failing to further limit the independent claims) is withdrawn due to arguments made by applicant on page 26 of the Remarks of 8 November 2006.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 18-22 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 18-22 are dependent from cancelled claim 17 and therefore are not complete (see M.P.E.P. section 608.01(n) part V). They will not be treated further on the merits.

Claims 34-65 and 70 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01.

Claim 34 recites the concluding limitation, "thereby providing said systemic property of said biochemical reaction network to a user," yet nowhere in the remainder of the claim does applicant disclose how a user is to be provided with the necessary information. Applicant concludes that the user obtains the information without providing a tangible mechanism for which the user is supplied with the information.

Claim Rejections - 35 USC § 101

The rejections of claims 71-74 under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter are withdrawn due to amendments made by the applicants to the set of claims filed on 8 November 2006.

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-16, 23-65, and 70 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

In regards to claims 1-16 and 23-33, a computer readable media with nonfunctional descriptive material is not a statutory type of invention. As stated in section 2106.01 in the MPEP:

> When nonfunctional descriptive material is recorded on some computer-readable medium, in a computer or on an electromagnetic carrier signal, it is not statutory since no requisite functionality is present to satisfy the practical application requirement. Merely claiming nonfunctional descriptive material, i.e., abstract ideas, stored on a computer-readable medium, in a computer, or on an electromagnetic carrier signal, does not make it statutory.

In the instant case, the program for analyzing reaction pathways does not have a functional role on the computer on which it operates, and therefore, the computer readable media containing this program does not constitute a statutory class of invention.

In regards to claims 1-16, 23-65, and 70, the instant claims are drawn to a computer readable medium comprising a program for analysis of a reaction network and a method for determining a systemic property of a biochemical network. A computer

readable medium comprising a program for analysis of a reaction network and a method for determining a systemic property of a biochemical network are non-statutory unless the claims include a step of physical transformation, or if the claims include a useful, tangible and concrete result. It is important to note, that the claims themselves must include a physical transformation step or a useful, tangible and concrete result in order for the claimed invention to be statutory. It is not sufficient that a physical transformation step or a useful, tangible, and concrete result be asserted in the specification for the claims to be statutory. In the instant claims, there is no step of physical transformation, thus the Examiner must determine if the instant claims include a useful, tangible, and concrete result.

In determining if the claimed subject matter produces a useful, concrete, and tangible result, the Examiner must determine each standard individually. For a claim to be "useful," the claim must produce a result that is specific, and substantial. For a claim to be "concrete," the process must have a result that is reproducible. For a claim to be "tangible," the process must produce a real world result. Furthermore, the claim must be limited only to statutory embodiments.

Claims 1-16, 23-65, and 70, do not produce a tangible result. A tangible result requires that the claim must set forth a practical application to produce a real-world result. This rejection could be overcome by amendment of the claims to recite that a result of the method is outputted to a display or a memory or another computer on a network, or by including a physical transformation.

As stated in M.P.E.P. section 2106, "The tangible requirement does not necessarily mean that a claim must either be tied to a particular machine or apparatus or must operate to change articles or materials to a different state or thing. However, the tangible requirement does require that the claim must recite more than a Sec. 101 judicial exception, in that the process claim must set forth a practical application of that Sec. 101 judicial exception to produce a real-world result. Benson, 409 U.S. at 71-72, 175 USPQ at 676-77 (invention ineligible because had "no substantial practical application."). "[A]n application of a law of nature or mathematical formula to a . . . process may well be deserving of patent protection." Diehr, 450 U.S. at 187, 209 USPQ at 8 (emphasis added); see also Corning, 56 U.S. (15 How.) at 268, 14 L.Ed. 683 ("It is for the discovery or invention of some practical method or means of producing a beneficial result or effect, that a patent is granted . . ."). In other words, the opposite meaning of "tangible" is "abstract.""

Claim Rejections - 35 USC § 102

The rejections of claims 1-2, 5-7, 23-26, 29, 32, 34, 40, 53-54, 56-61, and 64-66 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 00/46405 are withdrawn due to the change in the benefit date concerning this set of claims.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-2, 5-7, 23-26, 29, 32, 34, 40, 53-54, 56-61, and 64-66 are rejected under 35 U.S.C. 102(a) as being anticipated by WO 00/46405.

Claims 1-2, 5-7, 23-26, 29, 32, 34, 40, 53-54, 56-61, and 64-66 are rejected under 35 U.S.C. 102(e) as being anticipated by WO 00/46405.

Claims 1-2, 5-7, 23-26, 29, 32, 34, 40, 53-54, 56-61, and 64-65 state:

1. A computer readable medium or media, comprising: (a) a data structure stored on a computer readable medium or media relating a plurality of reactants to a plurality of reactions of a biochemical reaction network, wherein each of said reactions comprises a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating said substrate and said product, and wherein at least one of said reactions is a regulated reaction; and (b) a constraint set for said plurality of reactions, wherein said constraint set comprises a variable constraint for said regulated reaction and (c) commands for determining a flux distribution that minimizes or maximizes an objective function when said constraint set is applied to said data structure, wherein said at least one flux distribution determines a systemic property of said biochemical reaction network, wherein said systemic property is dependent upon the flux through said regulated region.

2. The computer readable medium or media of claim 1, wherein said variable constraint is dependent upon the outcome of at least one reaction in said data structure.

5. The computer readable medium or media of claim 1, wherein said variable constraint is dependent upon the presence of a biochemical reaction network participant.

6. The computer readable medium or media of claim 5, wherein said participant is selected from the group consisting of a substrate, product, reaction, protein, macromolecule, enzyme and gene.

7. The computer readable medium or media of claim 1, wherein said biochemical reaction network comprises metabolic reactions.

23. The computer readable medium or media of claim 1, wherein said data structure comprises a set of linear algebraic equations.

24. The computer readable medium or media of claim 1, wherein said data structure comprises a matrix.

25. The computer readable medium or media of claim 1, further comprising commands for representing said at least one flux distribution as a flux distribution map.

26. The computer readable medium or media of claim 1, wherein at least one reactant in said plurality of reactants or at least one reaction in said plurality of reactions is annotated.

29. The computer readable medium or media of claim 26, wherein said annotation comprises assignment to an open reading frame or protein.

32. The computer readable medium or media of claim 1, wherein said biochemical reaction network comprises reactions that are selected from the group consisting of glycolysis, the TCA cycle, the pentose phosphate pathway, respiration, biosynthesis of an amino acid, degradation of an amino acid, biosynthesis of a purine, biosynthesis of a pyrimidine, biosynthesis of a lipid, metabolism of a fatty acid, biosynthesis of a cofactor, metabolism of a cell wall component, transport of a metabolite and metabolism of carbon, nitrogen, sulfur, phosphate, hydrogen or oxygen.

34. A method for determining a systemic property of a biochemical reaction network, comprising: (a) providing a data structure relating a plurality of reactants to a plurality of reactions of a biochemical reaction network, wherein each of said reactions comprises a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating said substrate and said product, and wherein at least one of said reactions is a regulated reaction; (b) providing a constraint set for said plurality of reactions, wherein said constraint set comprises a variable constraint for said regulated reaction; (c) providing a condition-dependent value to said variable constraint; (d) providing an objective function, and (e) determining at least one flux distribution that minimizes or maximizes said objective function when said constraint set is applied to said data structure, wherein said at least one flux distribution is determinative of a systemic property of said biochemical reaction network, thereby providing said systemic property of said biochemical reaction network to a user.

40. The method of claim 34, wherein said biochemical reaction network comprises metabolic reactions.

53. The method of claim 34, wherein said flux distribution is determined by optimization.

54. The method of claim 53, wherein said optimization comprises linear optimization or non linear optimization.

56. The method of claim 34, wherein said data structure comprises a set of linear algebraic equations.

57. The method of claim 34, wherein said data structure comprises a matrix.

58. The method of claim 34, further comprising a step of producing a flux distribution map.

59. The method of claim 34, wherein said biochemical reaction network comprises reactions that are selected from the group consisting of glycolysis, the TCA cycle, pentose phosphate pathway, respiration, biosynthesis of an amino acid, degradation of an amino acid, biosynthesis of a purine, biosynthesis of a pyrimidine, biosynthesis of a lipid, metabolism of a fatty acid, biosynthesis of a cofactor, metabolism of a cell wall component, transport of a metabolite and metabolism of a carbon source, nitrogen source, oxygen source, phosphate source, hydrogen source or sulfur source.

60. The method of claim 34, wherein said systemic property is selected from the group consisting of growth, energy production, redox equivalent production, biomass production, production of biomass precursors, production of a protein, production of an amino acid, production of a purine, production of a pyrimidine, production of a lipid, production of a fatty acid, production of a cofactor, production of a cell wall component, transport of a metabolite, development, intercellular signaling, and consumption of carbon nitrogen, sulfur, phosphate, hydrogen or oxygen.

61. The method of claim 34, wherein said systemic property is selected from the group consisting of degradation of a protein, degradation of an amino acid, degradation of a purine, degradation of a pyrimidine, degradation of a lipid, degradation of a fatty acid, degradation of a cofactor and degradation of a cell wall component.

64. The method of claim 34, further comprising providing a gene database relating one or more reactions in said data structure with one or more open reading frames or proteins in a particular organism.

65. The method of claim 64, further comprising identifying an open reading frame that encodes a protein that performs a reaction in said plurality of reactions.

The invention of WO 00/46405, entitled, "Methods for identifying drug targets based on genomic sequence data," states in the Summary of the Invention on page 3:

This invention relates to constructing metabolic genotypes and genome specific stoichiometric matrices from genome annotation data. The functions of the metabolic genes in the target organism are determined by homology searches against databases of genes from similar organisms. Once a potential function is assigned to each metabolic gene of the target organism, the resulting data is analyzed. In one embodiment, each gene is subjected to a flux-balance analysis to assess the effects of genetic deletions on the ability of the target organism to produce essential biomolecules necessary for its growth.

Consequently, the systemic property and regulatory being analyzed is the ability of the target organism to produce essential biomolecules necessary for its growth.

The system of linear equations is denoted in Equation 1 of page 7 of WO 00/46405 in that the dot product of the stoichiometric matrix, S, and the flux vector, v is zero. Equations 2 and 3 on page 87 of WO 00/46405 describe how to minimize the objective function using linear optimization.

Equation 4 on page 8 of WO 00/46405 describes additional constraints which can be utilized in solving the linear systems of equations. These constraints are interpreted as variable constraints in that they can be represented by functions whose values, when acted upon by a function, are equal to a constant (see paragraphs [0048] and [0049] of the instant specification for the broad definitions of "variable" and "function").

Page 4 of WO 00/46405 describes the computer systems and computer languages on which the calculations are endeavored.

Pages 15-32 of WO 00/46405 illustrate flux distribution maps.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

35 U.S.C. 103 Rejection #1:

Claims 1-7, 9, 14-15, 23-24, 39-40, 42-45, 48-49, 51-61, 64-65, and 70-74 rejected under 35 U.S.C. 103(a) as being unpatentable over Blanch et al. [Biochemical Engineering, 1996, Marcel Dekker, Inc, New York, pages 1-14, and 33-35] in view of Alberty [Biophysical Journal, volume 71, 1996, pages 507-515].

Claims 1-7, 9, 14-15, 23-24, 39-40, 42-45, 48-49, 51-61, 64-65, and 70-74 state:

1. A computer readable medium or media, comprising: (a) a data structure stored on a computer readable medium or media relating a plurality of reactants to a plurality of reactions of a biochemical reaction network, wherein each of said reactions comprises a

reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating said substrate and said product, and wherein at least one of said reactions is a regulated reaction; and (b) a constraint set for said plurality of reactions, wherein said constraint set comprises a variable constraint for said regulated reaction and (c) commands for determining a flux distribution that minimizes or maximizes an objective function when said constraint set is applied to said data structure, wherein said at least one flux distribution determines a systemic property of said biochemical reaction network, wherein said systemic property is dependent upon the flux through said regulated region.

2. The computer readable medium or media of claim 1, wherein said variable constraint is dependent upon the outcome of at least one reaction in said data structure.

3. The computer readable medium or media of claim 1, wherein said variable constraint is dependent upon the outcome of a regulatory event.

4. The computer readable medium or media of claim 1, wherein said variable constraint is dependent upon time.

5. The computer readable medium or media of claim 1, wherein said variable constraint is dependent upon the presence of a biochemical reaction network participant.

6. The computer readable medium or media of claim 5, wherein said participant is selected from the group consisting of a substrate, product, reaction, protein, macromolecule, enzyme and gene.

7. The computer readable medium or media of claim 1, wherein said biochemical reaction network comprises metabolic reactions.

9. The computer readable medium or media of claim 8, wherein said regulatory data structure represents a regulatory event selected from the group consisting of transcription of a gene, translation of an RNA, post-translational modification of a protein, inhibition of a protein, activation of a protein, assembly of a protein, change in pH, change in redox potential, change in temperature, passage of time, and degradation of a protein.

14. The computer readable medium or media of claim 1, further comprising a constraint function that correlates an outcome of a regulatory event with said variable constraint.

15. The computer readable medium or media of claim 14, wherein said constraint function is binary.

23. The computer readable medium or media of claim 1, wherein said data structure comprises a set of linear algebraic equations.

24. The computer readable medium or media of claim 1, wherein said data structure comprises a matrix.

25. The computer readable medium or media of claim 1, further comprising commands for representing said at least one flux distribution as a flux distribution map.

26. The computer readable medium or media of claim 1, wherein at least one reactant in said plurality of reactants or at least one reaction in said plurality of reactions is annotated.

27. The computer readable medium or media of claim 26, wherein said annotation comprises assignment of said at least one reactant to a compartment.

28. The computer readable medium or media of claim 27, wherein a first substrate or product in said plurality of reactions is assigned to a first compartment and a second substrate or product in said plurality of reactions is assigned to a second compartment.

29. The computer readable medium or media of claim 26, wherein said annotation comprises assignment to an open reading frame or protein.

30. The computer readable medium or media of claim 26, wherein said annotation comprises a confidence rating.

31. The computer readable medium or media of claim 1, further comprising a gene database relating one or more reactions in said data structure with one or more genes or proteins in particular organism.

32. The computer readable medium or media of claim 1, wherein said biochemical reaction network comprises reactions that are selected from the group consisting of glycolysis, the TCA cycle, the pentose phosphate pathway, respiration, biosynthesis of an amino acid, degradation of an amino acid, biosynthesis of a purine, biosynthesis of a pyrimidine, biosynthesis of a lipid, metabolism of a fatty acid, biosynthesis of a cofactor, metabolism of a cell wall component, transport of a metabolite and metabolism of carbon, nitrogen, sulfur, phosphate, hydrogen or oxygen.

33. The computer readable medium or media of claim 1, wherein a plurality of said reactions are regulated reactions and said constraints for said regulated reactions comprise variable constraints.

34. A method for determining a systemic property of a biochemical reaction network, comprising: (a) providing a data structure relating a plurality of reactants to a plurality of reactions of a biochemical reaction network, wherein each of said reactions comprises a reactant identified as a substrate of the reaction, a reactant identified as a product of the

reaction and a stoichiometric coefficient relating said substrate and said product, and wherein at least one of said reactions is a regulated reaction; (b) providing a constraint set for said plurality of reactions, wherein said constraint set comprises a variable constraint for said regulated reaction; (c) providing a condition-dependent value to said variable constraint; (d) providing an objective function, and (e) determining at least one flux distribution that minimizes or maximizes said objective function when said constraint set is applied to said data structure, wherein said at least one flux distribution is determinative of a systemic property of said biochemical reaction network, thereby providing said systemic property of said biochemical reaction network to a user.

39. The method of claim 38, wherein said participant is selected from the group consisting of a substrate, product, reaction, enzyme, protein, macromolecule and gene.

40. The method of claim 34, wherein said biochemical reaction network comprises metabolic reactions.

42. The method of claim 41, wherein said regulatory event is selected from the group consisting of transcription of a gene, translation of an RNA, post-translational modification of a protein, inhibition of a protein, activation of a protein, assembly of a protein, change in pH, change in redox potential, change in temperature, passage of time, and degradation of a protein.

43. The method of claim 41, wherein said regulatory event is due to a signal transduction pathway.

44. The method of claim 41, wherein said biochemical reaction network and said regulatory data structure represent reactions or events that occur in a single cell.

45. The method of claim 41, wherein said regulatory event comprises a regulatory reaction.

48. The method of claim 41, further comprising a constraint function that correlates an outcome of a regulatory event with said variable constraint.

49. The method of claim 48, wherein said constraint function is binary.

51. The method of claim 48, wherein said constraint function correlates a first set of outcomes of said regulatory data structure with a first binary value and a second set of outcomes of said regulatory data structure with a second binary value.

52. The method of claim 48, wherein said constraint function correlates a set of outcomes of said regulatory data structure with a single integer value.

53. The method of claim 34, wherein said flux distribution is determined by optimization.

54. The method of claim 53, wherein said optimization comprises linear optimization or non linear optimization.

55. The method of claim 34, further comprising a step of modifying said data structure or said constraint set, or both.

56. The method of claim 34, wherein said data structure comprises a set of linear algebraic equations.

57. The method of claim 34, wherein said data structure comprises a matrix.

58. The method of claim 34, further comprising a step of producing a flux distribution map.

59. The method of claim 34, wherein said biochemical reaction network comprises reactions that are selected from the group consisting of glycolysis, the TCA cycle, pentose phosphate pathway, respiration, biosynthesis of an amino acid, degradation of an amino acid, biosynthesis of a purine, biosynthesis of a pyrimidine, biosynthesis of a lipid, metabolism of a fatty acid, biosynthesis of a cofactor, metabolism of a cell wall component, transport of a metabolite and metabolism of a carbon source, nitrogen source, oxygen source, phosphate source, hydrogen source or sulfur source.

60. The method of claim 34, wherein said systemic property is selected from the group consisting of growth, energy production, redox equivalent production, biomass production, production of biomass precursors, production of a protein, production of an amino acid, production of a purine, production of a pyrimidine, production of a lipid, production of a fatty acid, production of a cofactor, production of a cell wall component, transport of a metabolite, development, intercellular signaling, and consumption of carbon nitrogen, sulfur, phosphate, hydrogen or oxygen.

61. The method of claim 34, wherein said systemic property is selected from the group consisting of degradation of a protein, degradation of an amino acid, degradation of a purine, degradation of a pyrimidine, degradation of a lipid, degradation of a fatty acid, degradation of a cofactor and degradation of a cell wall component.

64. The method of claim 34, further comprising providing a gene database relating one or more reactions in said data structure with one or more open reading frames or proteins in a particular organism.

65. The method of claim 64, further comprising identifying an open reading frame that encodes a protein that performs a reaction in said plurality of reactions.

70. The method of claim 34, wherein a plurality of said reactions are regulated reactions

and said constraints for said regulated reactions comprise variable boundary values.

71. A method for determining a systemic property of a biochemical reaction network at a first and second time, comprising: (a) providing a data structure relating a plurality of reactants to a plurality of reactions of a biochemical reaction network, wherein each of said reactions comprises a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating said substrate and said product, and wherein at least one of said reactions is a regulated reaction; (b) providing a constraint set for said plurality of reactions, wherein said constraint set comprises a variable constraint for said regulated reaction; (c) providing a condition-dependent value to said variable constraint; (d) providing an objective function; (e) determining at least one flux distribution at a first time that minimizes or maximizes said objective function when said constraint set is applied to said data structure, thereby determining a systemic property of said biochemical reaction network at said first time; (f) modifying said value provided to said variable constraint, (g) repeating step (e), thereby determining a systemic property of said biochemical reaction network at a second time, and (h) providing said systemic property of said biochemical reaction network to a user at said first, second or first and second time.

72. The method of claim 71, wherein said value is modified based on said flux distribution at said first time.

73. The method of claim 71, wherein said value is modified based on a change in an environmental condition.

74. The method of claim 71, further comprising repeating steps (e) through (g) for a specified number of timepoints.

The book of Blanch et al., entitled, "Biochemical Engineering" provides a useful example in the first chapter on pages 13-14, entitled, "An example of intermediate in the reaction pathway: the mechanism of chymotrypsin," in which Blanch et al. states:

> Chymotrypsin is a serine protease that cleaves the amide linkages in proteins and peptides. It has a binding pocket which is selective for the aromatic residues of amino acids. The reaction occurs by the reversible formation of a Michaelis complex, followed by acylation of Ser-195 to give a tetrahedral acylenzyme intermediate... Chymotrypsin will also act as an esterase; we can write the elementary reaction steps in the following form, where RCO-X is an amide or an ester
>
> $$E + RCO\text{-}X \leftrightarrow RCO\text{-}X\cdot E \rightarrow RCO\text{-}E + XH \rightarrow RCOOH + E$$
>
> Where
> X = NH-R' (amide) or X = O-R' (ester) and RCO-E is the acyl-enzyme intermediate. This can written more simply as

$$E + S \leftrightarrow ES \rightarrow ES' \rightarrow E + P$$

Consequently, the above reaction scheme is a reaction pathway with multiple reactions, stoichiometic coefficients, substrates, and products. The first reaction is regulated in that it is reversible.

Paragraphs [0048] and [0049] of the instant specification state the following definitions of "constraint," "variable," and "function":

> [0048] As used herein, the term "constraint" is intended to mean an upper or lower boundary for a reaction. A boundary can specify a minimum or maximum flow of mass, electrons or energy through a reaction. A boundary can further specify directionality of a reaction. A boundary can be a constant value such as zero, infinity, or a numerical value such as an integer. Alternatively, a boundary can be a variable boundary value as set forth below.
>
> [0049] As used herein, the term "variable," when used in reference to a constraint is intended to mean capable of assuming any of a set of values in response to being acted upon by a function. The term "function" is intended to be consistent with the meaning of the term as it is understood in the computer and mathematical arts. A function can be binary such that changes correspond to a reaction being off or on. Alternatively, continuous functions can be used such that changes in boundary values correspond to increases or decreases in activity. Such increases or decreases can also be binned or effectively digitized by a function capable of converting sets of values to discreet integer values. A function included in the term can correlate a boundary value with the presence, absence or amount of a biochemical reaction network participant such as a reactant, reaction, enzyme or gene. A function included in the term can correlate a boundary value with an outcome of at least one reaction in a reaction network that includes the reaction that is constrained by the boundary limit. A function included in the term can also correlate a boundary value with an environmental condition such as time, pH, temperature or redox potential.

There are several constraints on the above system of reactions. The partial derivatives of ES and ES' concentration with respect to time are both zero indicating a steady state flux in complex association and dissociation. In addition, there is a constraint on mass balances of enzyme concentration indicated by the last reaction proposed on page 13 of Blanch et al.

$$[E_o] = [E] + [ES] + [ES']$$

By the definitions given by the applicant in the instant specification, the partial derivatives of complex concentrations with respect to time being equal to zero are variable constraints in that the partial derivatives are being equated with a function whose value is zero. These variable and/or boundary constraints also are commands and regulators of the flux distributions that minimize the objective functions (the partial derivatives of complex concentration with respect to time is minimized to a steady state condition)- they determine the final concentration of product as a function of time. The conditions governing the set of reactions listed comprise boundary values. The mass balance acts to conserve the amount of enzyme. The diagrammed reaction pathway acts as a flux distribution map. The steady state assumption is a binary decision in that either it exists, or the approximation in not steady state.

These "steady state conditions" are variable constraints dependent on the concentrations of the complexes in the system of reactions. These sets of chymotrypsin regulatory reactions are considered metabolic reactions. Chymotrypsin is an enzyme that is regulated by the binding of an amino acid ligand.

The second equation of reactions in this Office action annotates the enzyme as E (representing chymotrypsin), the substrate as S or S' (representing an amide or ester), and the product as P (representing a carboxylic acid). The enzyme is a protein and the reaction network involves biosynthesis of a cofactor.

For complete computations of product, the sets of reactions given in Blanch et al. must be solved over a range of time until product production reaches steady state with time.

However, Blanch et al. does not mention this function of chymotrypsin catalysis in the cell or in multicellular organisms. Additionally, Blanch does not teach the matrix or binary aspects of the claims. Blanch also does not teach the computer aspect of the instantly rejected set of claims.

The article of Alberty, entitled "Calculation of biochemical net reactions and pathways by using matrix operations" states in its abstract:

> Pathways for net biochemical reactions can be calculated by using a computer program that solves systems of linear equations.

Alberty states on lines 3-9 of page 2:

> The mathematics of systems of reactions is explored in the next section. Because of the mathematical character of the stoichiometry of biochemical equations, mathematical operations on them can be carried out on personal computers using mathematical programs such as Mathematica..., MATLAB..., and Maple... By use of computer programs for linear algebra, it is convenient to calculate new reactions and pathways even for large systems of biochemical reactions.

Alberty shows use of matrices with stoichiometric coefficients in equation 1 on page 3. Figure 1 on page 9 of Alberty shows a matrix of binary variables for a system of 21 reactions with 30 reactants. A value of "zero" indicates that the reactant is not present in the reaction, while a non-zero integer value indicates the presence of the reactant. Linear optimization is used to solve the system of linear equations for the metabolic process such as glycolysis described throughout Alberty. The variable constraint on the systems of reaction equations is the value of pH. As stated in the introduction, the specific value of pH affects the proton (i.e. H^+) balance in the chemical reactions.

Alberty shows in Table 1 on page 10 the different possible enzymes used to catalyze the metabolic reactions and their EC No. corresponding to an entry into a gene

and protein database. The equilibrium constants in Alberty are a direct indication of free energy of the reaction which is interpreted as a level of confidence by which this reaction occurs.

It would have been obvious at the time of the instant invention for someone of ordinary skill in the art to modify the chymotrypsin model of Blanch et al. by use of the computerized linear analysis methods of Alberty because while Blanch et al. describe the model which describes the method of the instant set of claims, Alberty extends this method to appropriate computer systems and programs useful for linear optimization of analogous, yet more complex biological metabolic processes.

35 U.S.C. 103 Rejection #2:

Claims 1, 8, 10-13, 34, 41, and 46-47 rejected under 35 U.S.C. 103(a) as being unpatentable over Blanch et al. in view of Alberty as applied to claims 1-7, 9, 14-15, 23-24, 39-40, 42-45, 48-49, 51-61, 64-65, and 70-74 above, and further in view of Grewal et al. [Protein Engineering, volume 7, 1994, pages 205-211].

Claims 10-13 and 46-47 state:

10. The computer readable medium or media of claim 8, wherein said regulatory event is due to a signal transduction pathway.

11. The computer readable medium or media of claim 8, wherein said biochemical reaction network and said regulatory data structure represent reactions or events that occur in a single cell.

12. The computer readable medium or media of claim 8, wherein said biochemical reaction network represents reactions that occur in a first cell in a population of cells and said regulatory data structure represents events that occur in a second cell in said population.

13. The computer readable medium or media of claim 12, wherein said population of cells comprises cells of a multicellular organism.

46. The method of claim 41, wherein said biochemical reaction network represents reactions that occur in a first cell in a population of cells and said regulatory data structure represents events that occur in a second cell in said population.

47. The method of claim 46, wherein said population of cells comprises cells of a multicellular organism.

Blanch et al. and Alberty as applied to claims 1-7, 9, 14-15, 23-24, 39-40, 42-45, 48-49, 51-61, 64-65, and 70-74 above, do not teach the use of chymotrypsin in cells or multicellular organisms. Additionally Branch et al. and Alberty do not mention signal transduction.

The article of Grewal et al., entitled, "Computer modeling of the interaction between human choriogonadotropin and its receptor," states in its introduction:

> The endocrine action of the ovarian luteinizing hormone (LH) and the placental choriogonadotropin (CG), is mediated by the LF/CG receptor. Binding of LH or CG to the receptor on gonadal target cells results in the increase in adenyl cyclase activity... which is mediated by membrane-associated intracellular G-proteins... Increase in cAMP concentration finally leads to steroid synthesis and secretion..., thus regulating gonadal functions. Hormonal recognition by the LH/CG receptor involves a site of interaction in the extracellular domain of the receptor...

Consequently, Grewal et al. describe a reaction pathway in a multicellular organism where the reaction in one cell mediates cellular interactions in the multicellular organism (i.e. signal transduction pathways).

Grewal et al. continues to describe the analogy between choriogonadotropins and chymotrysins in the section bridging columns 1 and 2 on page 205 by stating:

> The analogy of gonadotropins with serine proteases has been known since the late 1970s... It was adequately recognized that the sequences corresponding to the substrate-binding pocket of chymotrypsin have significant homology with those corresponding to the receptor binding site of hCG....

It would have been obvious for someone of ordinary skill in the art at the time of the instant invention to modify Blanch et al. in view of Alberty as applied to claims 1-7, 9, 14-15, 23-24, 39-40, 42-45, 48-49, 51-61, 64-65, and 70-74 above, and further in view of Grewal et al. because Grewal et al. has the advantage of teaching signal transduction and the interaction between receptors and ligands through computer modeling using the analogous enzyme of choriogonadotropin for the purpose of regulating gonadal function.

35 U.S.C. 103 Rejection #3:

Claims 1-16 and 23-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Edwards et al. [Journal of Biological Chemistry, volume 274, 1999, pages 17410-17416].

Claims 1-16 and 23-33 are a computer readable medium or media for storing and analysis of reaction pathway information.

The article of Edwards et al., entitled, "Systems properties of the Haemophilus Rd Metabolic groups," discloses a computer readable medium comprising a data structure and data. See abstract, results and Figures 2 and 3.

However, Edwards et al. does not discuss the specific methods analyzed by the computer programs.

The computer readable media differs from the method stated in the instant set of claims only by the computer program content on the computer readable media. The MPEP states in 2106.01:

> When nonfunctional descriptive material is recorded on some computer-readable medium, in a computer or on an electromagnetic carrier signal, it is not statutory and should be rejected under 35 U.S.C. 101. In addition, USPTO personnel should inquire whether there should be a rejection under 35 U.S.C. 102 or 103. USPTO personnel should determine whether the claimed nonfunctional descriptive material be given patentable weight. USPTO personnel must consider all claim limitations when determining patentability of an invention over the prior art. In re Gulack, 703 F.2d 1381, 1385, 217 USPQ 401, 403-04 (Fed. Cir. 1983). USPTO personnel may not disregard claim limitations comprised of printed matter. See Gulack, 703 F.2d at 1384, 217 USPQ at 403; see also Diehr, 450 U.S. at 191, 209 USPQ at 10. However, USPTO personnel need not give patentable weight to printed matter absent a new and unobvious functional relationship between the printed matter and the substrate. See In re Lowry, 32 F.3d 1579, 1583-84, 32 USPQ2d 1031, 1035 (Fed. Cir. 1994); In re Ngai, 367 F.3d 1336, 70 USPQ2d 1862 (Fed. Cir. 2004).

The above paragraph cites four court decisions which, when taken together, give the same message and theme regarding prior art and patentability of computerized media.

In *In re Gulack*, the CAFC ruled to give the appellant's claims patentability over the prior art because the mathematical educating device served as functional descriptive material, distinguishing it over the prior art.

As stated on page 1 of the decision:

> Printed matter that is not functionally related to substrate does not distinguish invention from prior art in terms of patentability; although printed matter must be considered, in that situation it may not be entitled to patentable weight.

In *In re Ngai*, the CAFC did not give patentable weight over the prior art to an identical process of amplifying ribonucleic acids with a distinct set of printed instructions to execute this process because this set of instructions is not functional and therefore does not serve to distinguish it over the prior art.

In *In re Lowry*, the CAFC gives functional data structures patentability, and distinguishes these data structures and computer memory from nonfunctional printed matter.

As stated on page 1 of the decision:

> Claims for data processing system are neither anticipated by, not obvious in view of, prior patent for database management system, since claimed invention, which employs plurality of attribute data objects having both hierarchical and non-hierarchical relationships, involves organization of information and its interrelationships which reference neither discloses nor suggests.

In *Diehr*, the US Supreme Court ruled analogously to the previous three cases with regards to mathematical equations. As stated at the bottom of page 10 of the ruling:

> when a claim containing a mathematical formula implements or applies that formula in a structure or process which, when considered as a whole, is performing a function which the patent laws were designed to protect (e.g., transforming or reducing an article to a different state or thing), then the claim satisfied the requirements of 35 U.S.C. 101.

The difference between Edwards et al. and the claimed invention constitutes non-functional descriptive material because the content of the computer readable media database does not alter how the computer system functions, i.e., the database of the claimed computer system does not reconfigure the computer system to perform a different function than the computer system of Edwards et al. Therefore, no patentable weight is given to the content of the database on the claimed computer system and its method of use.

Response to Arguments

Applicant's arguments filed 8 November 2006 have been fully considered but they are not persuasive.

Response to 35 U.S.C. 101 Rejections

Applicant traverses the 35 U.S.C. 101 rejections on pages 15-21 of the Remarks of 8 November 2006. All of the arguments are considered and are found not to be persuasive.

Applicant first argues on page 15 of the Remarks of 8 November 2006 that the amended independent claims in the instant rejection overcome the nonstatutory aspects of the claims. However, the amended claims do not impart functionality onto the computer for the instant set of claims.

Although applicants claim that their claimed invention in the instantly rejected set of claims is statutory, they refer to earlier rebuttals (i.e. the pages 15-17 of the Remarks of 4 April 2005) which cite obsolete sections of section 2106 of the M.P.E.P. and court decisions within this replaced section 2106 of the M.P.E.P.

Even taking into account these arguments from the replaced section of the M.P.E.P., the Office is not persuaded as to the statutory nature of the claims. Specifically, applicants cite previous section 2106 (IV)(B)(1) of the M.P.E.P. which refers to *In re Lowry* and *In re Warmerdam* in clarifying the boundaries of statutory subject matter. When looking into greater detail into these cases, it is elucidated what is meant by functionality of a computer algorithm. For example, on page 1034 of *In re Lowry*, the CAFC states:

> More than mere abstraction, the data structures are specific electrical or magnetic structural elements in a memory. According to Lowry, the data structures provide tangible benefits: data stored in accordance with the claimed data structures are more easily accessed, stored, and erased. Lowry further notes that, unlike prior art data structures, Lowry's data structures simultaneously represent complex data accurately and enable powerful nested operations. In short, Lowry's data structures are physical entities that provide increased efficiency in computer operation. They are not analogous to printed matter.

Furthermore, *In re Warmerdam* states:

> Dispositive issue in determining whether claims for method of controlling motion of objects and machines constitutes statutory subject matter pursuant to 35 U.S.C. 101 is whether process goes beyond simply manipulating "abstract ideas" or "natural phenomena;" claim which recited steps of "locating" medial axis, and "creating" bubble hierarchy, described nothing more than manipulation of basic mathematical constructs, even if claim implies physically measuring contours of object, and thus claim is unpatentable.

Taken together, instead of supporting the arguments of the applicant, these two decisions make clear the outcome that the instantly rejected claims are devoted to nonstatutory subject matter. *In re Lowry* illustrates that in order for an algorithm to be functional, it must affect the function of the computer on which it operates. *In re Warmerdam* illustrates that nonfunctional mathematical manipulations do not qualify as patentable matter.

Claims 1-16 and 23-33 recite limitations of a nonfunctional computer program which does not affect the operation of the computer readable medium or computer on which it operates, but instead has procedures and commands for manipulating reaction pathways. Under *Warmerdam*, these manipulations do not qualify as patentable matter.

Applicant continues to argue on pages 17-18 of the Remarks of 8 November 2006 that as conclude in the decision of *In re Lundgren*, the technological arts test cannot be used to determine the statutory nature of the claimed invention. However, this "technological arts test," in accordance with Annex III of the Interim Guidelines of 22 November 2005, is not being used to reject the claims of the instant invention.

With regard to claims 34-65 and 70, applicants argue on pages 18-19 of the Remarks of 8 November 2006 that the amendment to claim 34 makes claim 34 and the

claims dependent from it statutory. The conclusion to claim 34 states, "thereby providing said systemic property of said biochemical reaction network to a user." However, there is no element in the instant claim illustrating how the provision of said systemic property of said biochemical reaction network to a user occurs. In other words, applicant inherently assumes with the term "thereby" that the required tangible outcome occurs without stating the tangible outcome. In the absence of such a tangible step, this set of claims is accordingly considered both nonstatutory and indefinite (see 35 U.S.C. 112 section).

35 U.S.C. 102 Rejection:

The arguments of applicants concerning the anticipatory prior art rejections on pages 27-28 of the Remarks of 8 November 2006 have been considered and are found to not be persuasive.

Applicant first argues that the program on the computer readable is statutory media and should be given patentable weight. Even giving each step in the set of claims patentable weight, WO 00/46405 anticipates each step of the claim.

Applicants next argue that WO 00/46405 fails to describe a variable constraint for a regulated reaction as claimed. However, as the terms "variable" and "function" are defined in the instant specification, the constraints taught in WO 00/46405 are considered variable constraints (see the rejection above).

Applicant next cites paragraphs [0033] and [0061] in the instant specification in restricting what is meant by function and Boolean logic. In reciting the description of a

function, applicant states that it "is capable of assuming any of a set of values in response to being acted upon by a function." Applicant continues on page 28 of the Remarks of 8 November 2006 by stating by stating the functions can be represented by Boolean variables. While the dependent claims using Boolean logic have not been rejected in this rejection, the recitation of the specification dictates that the network of Boolean variables CAN BE introduced, but are not necessarily introduced.

35 U.S.C. 103 Rejection #3:

The arguments of applicants concerning the obviousness prior art rejections on pages 28-29 of the Remarks of 8 November 2006 have been considered and are found to not be persuasive.

Applicants argue that the steps of the instant set of claims are non-functional descriptive material and therefore should be given patentable weight. However, for the reasons described in the nonstatutory rejection, the nonfunctional descriptive material is not given patentable weight and should not be considered.

Consequently, the obviousness prior art rejection is sustained.

Conclusion

No claim is allowed.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the central PTO Fax Center. The faxing of such pages must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The Central PTO Fax Center Number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Negin, Ph.D., whose telephone number is (571) 272-1083. The examiner can normally be reached on Monday-Friday from 7am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor, Irem Yucel, Supervisory Patent Examiner, can be reached at (571) 272-0781.

Information regarding the status of the application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information on the PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RSN
20 February 2007

20 February 2007

20 February 2007

JOHN S. BRUSCA, PH.D
PRIMARY EXAMINER